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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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CAROL L FRANCIS
BOZICEVIC FIELD & FRANCIS LLP
200 MIDDLEFIELD ROAD
SUITE 200
MENLO PARK CA 94025

EXAMINER	
SCHNIZER,R	
ART UNIT	**PAPER NUMBER**
1632	10

DATE MAILED: 11/17/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

FILE COPY

Office Action Summary	Application No. 09/330,903	Applicant(s) Gonda et al
	Examiner Richard Schnizer	Group Art Unit 1632

☒ Responsive to communication(s) filed on *Aug 28, 2000*

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-20* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-20* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

An amendment was received and entered as Paper No. 9 on 8/28/00. Claims 1-20 are pending and under consideration in this office action.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

> The second application (which is called a continuing application) must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the continuing application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *In re Ahlbrecht*, 168 USPQ 293 (CCPA 1971).

In this case, claims 2, 6, and 7 of the instant application are not supported by the specification of the parent application. Specifically, the parent application, now issued as US Patent 5,906,202, does not clearly contemplate targeting aerosols to the alveoli, or of the use of lipids or liposomes. Applicant argues that '202' states that "particular areas of the lung are targeted" at column 2, lines 12-14, and further states that areas of the lung include an "alveolated region" at column 8, lines 61-62. However, these widely separated statements do not imply that the alveolated areas of the lung should be targeted by aerosols. In fact, there is no explicit or implicit support for targeting the alveoli.

Applicant further argues that the phrase "any pharmaceutically acceptable flowable liquid which is compatible with the active agent" provides support for the use of liposomes. The specification of '202' fails to mention the words "lipid" or "liposome", and fails to clearly describe any lipidic or liposomal formulation.

For these reasons, claims 2, 6, and 7 do not receive the benefit of the '202' filing date.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 8 and 9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 8 and 9, as amended, recite the step of heating an aqueous solution comprising a nucleic acid formulation prior to aerosolizing the formulation. Applicant relies on page 24, line 27 to page 25, line 7 to support this amendment. However, when considering the entire paragraph bridging pages 24 and 25, it is clear that the heating step is intended to take place only after aerosolization. The specification states that the size of the particles is subject to change by

evaporation "from the period of time from the formation of the aerosolized particles until the particles actually contact the lung surface". This appears to be accomplished by heating the atmosphere comprising the aerosol. See sentence bridging pages 24 and 25. The specification does not clearly contemplate heating, prior to aerosolization, an aqueous solution which comprises a nucleic acid formulation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-16 are indefinite because it recites the phrase "an aerodynamic diameter range designed to travel to an end location". An aerodynamic diameter range is a numerical value, not an object, and cannot physically travel to any location.

Claims 3, 4, and 20 are indefinite because it is not clear exactly where the upper respiratory tract ends, and the central airways begin, thus one of skill in the art is not apprised of the metes and bounds of the claim. Applicant argues that these terms are defined in the specification at page 14, lines 11-22. However, the definitions of these terms are not limiting and do not distinguish between the terms. For example, the central airways are defined as those

regions "which during normal breathing substantially remove particles larger than 3 microns in diameter. This description applies equally well to the upper respiratory tract. In any case, the question is where does the upper respiratory tract end, and the central airways begin? The specification does not define any boundary between these two regions, so the rejection is maintained.

Claims 17-19 are indefinite because it is unclear what is intended by "calibrating a delivery device based on the inspiratory volume determined in step (a)". It is unclear in what way the device should be calibrated. It is suggested that step (b) should be amended to recite "calibrating a delivery device to deliver the inspiratory volume determined in step (a)". These claims are also indefinite because the methods omit essential steps. Specifically, the methods recite no step at which the delivery device is used. It is suggested that step (d) should be amended to recite "using the calibrated delivery device to inhale the aerosolized particles into the respiratory tract of the subject, ...". The purpose of step (e) is also unclear. It is suggested that step (e) should be amended to recite "repeatedly aerosolizing the polynucleotide formulation at the same determined inspiratory volume as in step (c), and inhaling the aerosolized particles as in step (d)".

Claim 20 is indefinite because it lacks an essential method step. Claim 20 fails to recite any step in which particles are formed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-3, and 5-7, stand rejected under 35 U.S.C. 102(e) as being anticipated by Debs (US Patent 5,756,353, effective filing date of 12/17/91).

Debs teaches methods of delivering polynucleotides preferentially to specified regions of the respiratory tract wherein liquid DNA/cationic liposome formulations are aerosolized and inhaled into the respiratory tract of a subject. See abstract; column 5, lines 51-60; column 10, lines 53-59; and column 12, lines 3-5. For delivery to the alveoli and airways, preferred particle sizes are 0.2-2.0 μm and 5-10 μm, respectively. See column 12, lines 37-61; and claims 14-16, column 16.

The claims have been amended to recite a Markush group of delivery destinations consisting of "the upper respiratory tract, the central airways, and the alveoli". Applicant argues that the cited art does not anticipate the claims as amended because Debs fails to distinguish between the upper respiratory tract and the central airways. The rejection is proper because the prior art anticipates at least one species of the Markush group. Specifically, Debs anticipates targeting to the alveoli. A generic claim cannot be allowed if the prior art discloses species falling within the claimed genus. See MPEP 2131.02.

Applicant also asserts that the range of particle sizes cited in the office action (Paper No. 8) does not meet the range selected for targeting the alveoli according to the instant invention. The instant invention recites a range of particle sizes from "about 1-3" microns. The cited art recites a particle ranges of 0.2-2 microns for targeting the alveoli. See column 12, lines 43-47. At worst, these ranges overlap, so Debs teaches a set of particles which anticipates those of the instant invention. However, it is unclear what are the metes and bounds of "about 1-3" microns. Because 0.2 microns is reasonably close to 1 micron, and 2 microns is reasonably close to 3 microns, Debs can be considered to teach the precise range recited in the claim.

Thus Debs anticipates the claims.

Claims 1, 2, 6, 7, and 10 stand rejected under 35 U.S.C. 102(e) as being anticipated by Eljamal et al (US Patent 5,994,314, effective filing date of 4/7/93).

Eljamal teaches methods of delivering polynucleotides to the lung wherein dried, powdered DNA/cationic lipid complexes are aerosolized and inhaled. The preferred aerodynamic diameter of the complexes is 1-4 μm. See abstract; column 2, lines 24-35; column 5, lines 48-57; column 6, lines 30-33; and column 7, lines 22-34. It is noted that Eljamal does not explicitly disclose targeting of the alveolar region, however this targeting is inherent in the size range of the particles (1-4 μm).

Applicant argues that the cited art does not anticipate the claims as amended because Eljamal fails to distinguish between the upper respiratory tract and the central airways. The

rejection is proper because the prior art anticipates at least one species of the Markush group. Specifically, Eljamal anticipates preferential delivery to the alveoli. A generic claim cannot be allowed if the prior art discloses species falling within the claimed genus. See MPEP 2131.02.

Applicant further argues that the preferred range of 1-4 microns would not be specific to the alveoli. However, the claims do not require specific delivery to the alveoli. The claims require "preferential" delivery. Because the range of 1-4 microns overlaps the range of "about 1-3" microns recited in claim 2 for delivery to alveoli, Eljamal anticipates the claims. Furthermore, because it is unclear what are the metes and bounds of a range of "about 1-3" microns, and because 3 microns can reasonably be considered to be "about 4" microns, Eljamal can be considered to teach the precise range recited in the claim.

Thus Eljamal anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 12-15, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Debs (US Patent 5,756,353, effective filing date of 12/17/91), Lloyd et al (US Patent 5,497,763, effective filing date of 5/21/93), and Radhakrishnan (US Patent 5,049,389, issued 9/17/91).

Debs teaches methods of delivering polynucleotides preferentially to specified regions of the respiratory tract wherein aqueous DNA/cationic liposome formulations are aerosolized and inhaled into the respiratory tract of a subject. More specifically, Debs teaches that particular sites in the lung can be targeted by varying the size of the aerosol particles, and that particle size can be controlled by selection of an appropriate nebulizer. See abstract; column 5, lines 51-60; column 10, lines 53-59; and column 12, lines 3-5. Preferred particle size for delivery to the alveoli is 0.2-2.0 μm; and for the airways or nasopharynx, preferred particle size is 5-10 μm. See column 12, lines 37-61; and claims 14-16, column 16. Debs also contemplates delivery to the alveoli, trachea, pharynx, and bronchi. See column 12, lines 37-39. Debs does not teach ranges of about 4-6, and 7-10 μm for targeting the central airways and the upper respiratory tract, respectively.

Lloyd teaches a method for producing aerosol particles of any desired size in the range of 0.5 to 50 microns. The method involves forcing a formulation through a porous membrane, wherein the size of the aerosol particles formed is directly related to the diameter of the membrane pores. See column 24, lines 30-43. Applicant was unable to find in the specification of Lloyd any reference to particles in the range of 5-50 **mm**. This was due to a typographical error in the office action, specifically a failure to convert the first 'm' in "mm" to a symbol font. The correct size range was 5-50 **μm** as in the cited passage of Lloyd. In any event the range of 0.5-12 microns recited in Applicant's arguments is sufficient to cover the breadth of the particle sizes claimed in the instant application, thus Lloyd teaches methods of making aerosol particles of any desired size in the range of 0.5 to 12 microns.

Radhakrishnan teaches that aerosol droplets larger than 3 μm will reach the secondary bronchi, but not the alveoli. Droplets smaller than 3 μm will target the alveoli. See entire document, especially column 3, line 61 to column 4 line 1; column 15, lines 61-65; and column 16, lines 44 and 45. Radhakrishnan also presents a model depicting the relationship between aerosol particle aerodynamic diameter and penetration into the respiratory tract, thus providing the information required to target any region of the respiratory tract with particles of defined sizes. See Fig. 3. Applicant was unable to find any teaching by Radhakrishnan that suggests that particles of smaller than 3 microns will reach the alveoli, and suggests that Radhakrishnan actually teaches that particles of 1.1-2.1 microns will not reach the alveoli. The examiner apologizes for inadvertently omitting the specific passages supporting his position. As shown at column 3, line 61 to column 4 line 1; column 15, lines 61-65; and column 16, lines 44 and 45, Radhakrishnan clearly teaches that particles less than 3 microns in size, specifically particles of 1.1-2.1 microns, are expected to reach the alveoli.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the information provided in Fig. 3 of Radhakrishnan to selectively target the alveoli, central airways, or upper respiratory tract with the polynucleotide-containing aerosol particles of Debs. Although the relationship between particle diameter and lung target tissue taught by Radhakrishnan is not precisely the same as that disclosed in the instant invention, it is standard procedure, and well within the ability of one of ordinary skill, to optimize parameters such as aerosol particle diameter in order to achieve targeting to a specific tissue. One could have relied

on the teachings of Lloyd to produce particles of the appropriate size. One would have been motivated to target each of the claimed areas of the lung in order to maximize the delivery of polynucleotides to tissues *in vivo*. For example, it is well known in the art that the major obstacles to gene therapy, such as that proposed by Debs (column 1, lines 15-18), are insufficient delivery and expression of therapeutic polynucleotides. Thus one of ordinary skill in the art would seek to solve these problems by contacting as much of the respiratory tract as possible with polynucleotide-containing aerosol particles.

Applicant argues that none of the cited references provides motivation to produce particles of the claimed size ranges. This is unpersuasive in light of column 12, lines 37-39 of Debs, which contemplates delivery to such regions as the alveoli, pharynx, bronchi, and nasopharynx. Radhakrishnan teaches what size particles will reach each of these areas, and Lloyd teaches how to make particles of these sizes. Thus, the knowledge required to perform the claimed methods was available in the prior art, and delivery to the regions of the respiratory system in the central airways (bronchi), the upper respiratory tract (nasopharynx), and the alveoli had been contemplated at the time of the invention.

Thus the invention as a whole was *prima facie* obvious.

Claims 8, 9, 10, 11, and 16-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Debs , Lloyd et al (US Patent 5,497,763), and Radhakrishnan, as applied to claims 1-4, 12-

15, and 20 above, and further in view of Lloyd et al (US Patent 5,522,385, filed 9/27/94), and Lanpher et al (US Patent 5,333,106, issued 7/26/94).

The teachings of Debs, Lloyd '763', and Radhakrishnan are summarized above. Briefly these references can be combined to teach methods of delivering polynucleotides to various target regions of the respiratory system. The method entails converting into an aerosol an aqueous composition comprising nucleic acids. The nucleic acids can be associated with liposome particles. The size of the aerosol particles is controlled in order to target various regions of the respiratory system upon inhalation. Lloyd '763' also teaches a method of delivering aerosolized formulations wherein a delivery device is calibrated based on the electrically measured inspiratory volume of a subject. The calibration allows reproducible delivery of the formulation. See column 19, line 62 to column 20 line 4; and column 29, lines 12-25. These references do not teach heating the composition comprising the nucleic acids prior to forming the aerosol, the delivery of powdered aerosolized particles, targeting the region of the respiratory tract by adjusting the volume of air inhaled with the aerosol, or coaching the subject to inhale a given amount.

Lloyd '385' teaches a device and method for delivering powdered aerosolized particles to the lung wherein particles of 0.5-12.0 μm diameter are produced by extrusion through a porous membrane with pores of 0.25-6.0 μm diameter. The formulation comprising the particles to be aerosolized can be heated in order to evaporate carrier and to control the size of the particles. See claim 7, column 24; and column 11, lines 60-67. See also Fig. 1. Note that element 13, which is the heating mechanism, is located upstream of the membrane used to form the aerosol

(element 14 of Fig. 1). This allows heating of the formulation prior to aerosol formation. Alternatively, the particles may be heated after aerosol formulation by element 5, which is located downstream of the aerosolization membrane. See column 9, lines 28-38. This technique allows one to adjust particle dryness and size while accounting for environmental conditions such as relative humidity. Lloyd '385' also teaches a method of delivering aerosolized formulations wherein a delivery device is calibrated based on the electrically measured inspiratory volume of a subject. The calibration allows reproducible delivery of the formulation. See column 9, lines 15-26.

Lanpher is pertinent to claims 9 and 11. Lanpher teaches an electronic apparatus for measuring inspiration volume and airflow, and a method for teaching patients to inspire a particular volume at a particular rate. The purpose of the apparatus and the method is to teach patients to use aerosol inhalers properly so that medication is delivered to a target site in the patient's lungs. See entire document; especially abstract; paragraph bridging columns 8 and 9; column 9, lines 33-53; and claim 1, columns 24 and 25.

It would have been obvious to one of ordinary skill in the art at the time of the invention to adjust heat the aqueous compositions comprising polynucleotides, taught by Debs , Lloyd '763', and Radhakrishnan, prior to the formation of an aerosol, as taught by Lloyd '385'. One would have ben motivated to do so in order to adjust particle size in order to account for unusually high or low ambient humidity, or to deliver the composition as an aerosolized powder as taught by Lloyd '385'. See Lloyd '385' column 11, lines 60-67.

It would have been obvious to one of ordinary skill in the art at the time of the invention to adapt the device of Lanpher to train patients to use the delivery method of Lloyd '385' in order to target a specific site in the respiratory tract by adjusting the volume of air inhaled. One would have been motivated to do so because Lanpher teaches that many patients use inhalers improperly, thus there is a need to effectively train them in proper technique. See paragraph bridging columns 2 and 3. Lanpher specifically teaches adjusting inhalation to target a site in a patients lungs. See claim 1, columns 24 and 25.

Thus the invention as a whole was *prima facie* obvious.

Conclusion

No claim is allowed. Claims 16-19 are free of the art of record.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday-Friday from 7:30 to 4:00 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached at 703-305-6608. The FAX phone numbers for art unit 1632 are 703-308-4242 and 703-305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Richard Schnizer, Ph. D.

Karen M. Hauda

KAREN M. HAUDA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600